UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,947	09/09/2003	Sean C. Semple	INEX.P-003-3	3517

21121 7590 11/07/2005

OPPEDAHL AND LARSON LLP
P O BOX 5068
DILLON, CO 80435-5068

EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,947	SEMPLE ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A preliminary amendment filed 9/9/03 amended the specification, canceled claims 1-84 and added new claims 85-108.

Claims examined on the merits are 85-108, which are all claims in the application.

Agrawal and Bailey et al on page 2 of form 1449 of 2/13/04 have been lined through and not considered since copies did not accompany the form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 85-93, 97-106, and 108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to support using an amino lipid in producing nucleic acid-lipid particles when the amino lipid is not a titratable lipid having a pK_a as required in claim 1 of parent patent 6,858,225 B2 or a lipid containing protonatable or deprotonatable group having a pK_a as required in claim 1 of parent patent 6,287,591

B1. See the summary of the invention and the paragraph bridging pages 16 and 17 in the specification.

Support is not found in the specification for the nucleic acid-lipid particle not being substantially degraded at a temperature and time as required by claims 103 and 104. Example 10 disclosing that free phosphorothioate oligodeoxynucleotide shows significant breakdown in serum within 30 minutes is inadequate support. A time of 20 minutes is not found in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 89-93, 95, 96 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 89-93 are confusing by requiring percent cholesterol, amino lipid, neutral lipid and PEG-DAG conjugate of total lipid present, and not being clear as to lipids that constitute the total lipid present. Without knowing lipids that form the total lipids, a percent of the total cannot be determined.

Claims 95 and 96 are unclear by depending on claim 85, and not being clear how the nucleic acid-lipid particle of claim 85 is further

limited. Claim 95 requires sterol and a PEG-DAG conjugate already required in claim 85. To be clear, a dependent claim should set forth only components not in a previous claim, and not again require components that have been recited in the previous claim. Additionally, claim 95 should set forth which lipid in claim 85 is DODMA, and which is DSPC. See the form used by claims 86 and 94. The type of comments set forth in regard to claim 95 also applies to claim 107.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 85-93, 97-106 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wheeler et al (6,586,410 B1) in view of Collins (6,355,267 B1) and Cullis et al (6,417,326 B1) and Wheeler et al (WO 96/40964).

The claims are drawn to a nucleic acid-lipid particle comprising a nucleic acid, an amino lipid, a neutral lipid, a sterol and a polyethyleneglycol-diacylglycerol (PEG-DAG) conjugate. In dependent claims, the amino lipid is DODAP or DODMA, the neutral lipid is POPC or DSPC and the sterol is cholesterol.

Wheeler et al ('410) disclose a nucleic acid-lipid particle containing a nucleic acid, DODMA as a cationic lipid (col 51, line 64), DOPE or POPC as a non-cationic lipid (col 52, line 4), and a PEG-lipid such as a PEG-ceramide (col 52, lines 10-11). Sterols may also be present (col 8, line 67).

Collins discloses diacylglycerol (col 4, line 45) as a lipid that can be used to produce liposomes (col 4, line 32).

Cullis et al disclose producing liposomes (col 2, line 46) containing a bilayer stabilizing component which can be a lipid derivative such as polyethylene glycol (PEG) conjugated to ceramide (col 14, lines 22-29) or a peptide coupled to polyethylene glycol (col 15, lines 29-34) or a peptide having a covalently attached lipid such as diacylglycerol (col 16, lines 46-57 and col 18, line 54) to form a lipopeptide (col 3, lines 23-25).

Wheeler et al (WO) disclose lipid-nucleic acid particles containing a cationic lipid such as DODAC (page 15, line 16), which is

an amino lipid, and a non-cationic lipid such as POPC or DOPE (page 16, line 5), which is a neutral lipid. Also present, may be a polyethylene glycol-lipid conjugate such as a PEG-ceramide conjugate (page 81, claims 22 and 23). As shown in Table 2 (page 54), the lipid-nucleic acid particle may contain DOPE (neutral lipid), DODAC (amino lipid), cholesterol (sterol) and PEG-CerC14. The lipid-nucleic acid particles can be used to treat a patient by gene therapy to suppress gene expression (paragraph bridging pages 42 and 43).

It would have been obvious to use diacylglycerol as the lipid of the PEG-lipid contained by the lipid-nucleic acid particles of Wheeler et al ('410) as suggested by Collins disclosing using diacylglycerol as a lipid for preparing liposomes and Cullis et al disclosing preparing liposomes containing PEG coupled to a lipid or a peptide coupled to PEG, or a peptide coupled to diacylglycerol as bilayer stabilizing component. Selecting a preferred lipid from lipids known for use in liposomes to prepare the PEG-lipid of Wheeler et al ('410) would have been within the skill of the art and obvious. The PEG-DAG resulting from using diacylglycerol would have been expected to provide the function of a PEG-lipid desired by Wheeler et al ('410). It would have been further obvious to provide a sterol such as cholesterol in the nucleic acid-lipid particle of Wheeler et al ('410) as suggested by Wheeler et al (WO) disclosing a similar particle containing cholesterol and since Wheeler et al ('410) disclose that sterols can be present. The conditions of dependent claims would have

been matters of optimization determined by limited routine experimentation within the skill of the art.

Claim Rejections - 35 USC § 103

Claims 94-96 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 85-93, 97-106 and 108 above, and further in view of Unger (6,143,276).

The claims require the neutral lipid to be distearoylphosphatidylcholine (DSPC).

Unger discloses preparing lipid vesicles (col 12, lines 63-67), and discloses DSPC (col 13, line 18) as a lipid that can be used in preparing the vesicles.

When using PEG-DAG as the PEG-lipid of Wheeler et al ('410) as set forth above, it would have been obvious to use DSPC as the non-cationic lipid of Wheeler et al ('410) as suggested by Unger disclosing DSPC as a lipid that can be used in preparing a lipid vesicle.

Claim Rejections - 35 USC § 103

Claims 85-93, 97-106 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wheeler et al (WO 96/40964) in view of Collins and Cullis et al.

The invention and references are described above.

It would have been obvious to use diacylglycerol as the lipid of the PEG-lipid contained by the nucleic acid-lipid particle of Wheeler et al (WO) as suggested by Collins and Cullis et al for reasons set forth above when applying these references. The PEG-DAG resulting

from using diacylglycerol would have been expected to provide the function of a PEG-lipid desired by Wheeler et al (WO).

Claim Rejections - 35 USC § 103

Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 85-93, 97-106 and 108 above, and further in view of Unger ('276).

The claim requires DSPC as the neutral lipid.

Unger is described above.

When using PEG-DAG as the PEG-lipid of Wheeler et al (WO) as set forth above, it would have been obvious to use DSPC as the non-cationic lipid of Wheeler et al (WO) as suggested by Unger using DSPC in preparing a lipid vesicle.

Claim Rejections - 35 USC § 103

Claims 95, 96 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claim 94 above, and further in view of Wheeler et al ('410).

The claims require DODMA as the amino lipid in combination with DSPC.

When using DSPC as the non-cationic lipid of Wheeler et al (WO) as set forth above, it would have been obvious to use DODMA as the cationic lipid as suggested by Wheeler et al ('410) using DODMA as a cationic lipid in a lipid-nucleic acid particle similar to that of Wheeler et al (WO).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 85-93, 97-106 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,586,410 B1 in view of Collins and Cullis et al and Wheeler et al (WO).

It would have been obvious to use diacylglycerol as the lipid of the PEG-lipid contained by the nucleic acid-lipid particle of the patent claims as suggested by Collins and Cullis et al for reasons set forth above when applying these references. It would have been further obvious to provide cholesterol as a sterol in the nucleic acid-lipid particle of the patent claims as suggested by Wheeler et al (WO) disclosing a similar particle containing cholesterol.

Double Patenting

Claims 94-96 and 107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,586,410 B1 in view of the references as applied to claims 85-93, 97-106 and 108 above, and further in view of Unger (6,143,276).

For reasons set forth above when applying Unger, it would have been obvious to use DSPC as the non-cationic lipid contained by the nucleic acid-lipid particle of the patent claims as suggested by Unger.

Double Patenting

Claims 85-93, 97-106 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,858,225 B2 in view of Collins and Cullis et al and Wheeler et al (WO).

For reasons set forth above when applying Collins and Cullis et al, it would have been obvious to use diacylglycerol as the lipid of the PEG-lipid contained by the lipid-nucleic acid particles of the patent claims as suggested by Collins and Cullis et al. It would have been further obvious to combine a neutral lipid and a sterol such as cholesterol with the amino lipid and PEG-lipid of the patent claims as suggested by Wheeler et al (WO) disclosing lipid-nucleic acid particles containing a non-cationic lipid such as POPC or DOPE and cholesterol in combination with an amino-lipid and a PEG-lipid.

Double Patenting

Claims 94-96 and 107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,858,225 B2 in view of the references as applied to claims 85-93, 97-106 and 108 above, and further in view of Wheeler et al ('410) and Unger ('276).

It would have been obvious to use DODMA as the amino-lipid of the patent claims as suggested by Wheeler et al ('410) using DODMA (col 51, line 64) as a component of a nucleic acid-lipid particle similar to that of the patent claims. When providing a neutral lipid in the nucleic acid-lipid particle of the patent claims as set forth above, it would have been obvious to use DSPC as the neutral lipid as suggested by Unger disclosing using DSPC in preparing a lipid vesicle.

Double Patenting

Claims 85-94, 97-106 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,287,591 B1 in view of Collins and Cullis et al.

For reasons set forth above when applying Collins and Cullis et al, it would have been obvious to use diacylglycerol as the lipid of the PEG-lipid contained by the lipid-nucleic acid particles of the patent claims.

Double Patenting

Claims 95, 96 and 107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-72 of U.S. Patent No. 6,287,591 B1 in view of the references as applied to claims 85-94, 97-106 and 108 above, and in further view of Wheeler et al ('410).

It would have been obvious to use DODMA as the amino-lipid of the patent claims as suggested by Wheeler et al ('410) using DODMA (col 51, line 64) as a component of a nucleic acid-lipid particle similar to that of the patent claims.

Double Patenting

Claims 85-93, 97-106 and 108 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,734,171 B1 in view of Collins and Cullis et al and Wheeler et al (WO).

The patent claims a method of encapsulating a nucleic acid in a lipid bilayer containing DODAC, PEG-lipid and DOPE. See claims 1, 5, 6, 7 and 14.

It would have been obvious to use diacylglycerol as the lipid of the PEG-lipid of the patent claims as suggested by Collins and Cullis et al for reasons set forth above. The PEG-DAG resulting from using diacylglycerol would have been expected to provide the function of the PEG-lipid of the patent claims. It would have been further obvious to provide cholesterol (sterol) in the lipid bilayer of the patent claims as suggested by Wheeler et al (WO) disclosing a similar lipid bilayer containing cholesterol. It would have been expected cholesterol will function in the lipid bilayer of the patent claims as in the lipid bilayer of Wheeler et al.

Double Patenting

Claim 94 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,734,171 B1 in view of the references as applied to claims 85-93, 97-106 and 108 above, and further in view of Unger ('276).

When forming the lipid bilayer of the patent claims containing PEG-DAG and cholesterol as set forth above, it would have been obvious to use DSPC in place of the DOPE of the patent claims since DSPC is a neutral lipid like DOPE, and DSPC would have been expected to provide the function of DOPE.

Double Patenting

Claims 95, 96 and 107 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,734,171 B1 in view of the references as applied to claim 94 above, and further view of Wheeler et al ('410).

When forming the lipid bilayer of the patent claims containing DSPC as set forth above, it would been obvious to substitute DODMA for DODAC of the patent claims as suggested by Wheeler et al ('410) using DODMA in a lipid bilayer similar to that of the patent claims. DODMA is a cationic lipid like the DODAC of the patent claims, and DODMA would have been expected to provide the function of DODAC.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff

whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David M. Naff
Primary Examiner
Art Unit 1651

DMN
11/2/05